

Gene therapy-corrected autologous hepatocyte-like cells from induced pluripotent stem cells for the treatment of pediatric single enzyme disorders

Grant Award Details

Gene therapy-corrected autologous hepatocyte-like cells from induced pluripotent stem cells for the treatment of pediatric single enzyme disorders

Grant Type: Early Translational IV

Grant Number: TR4-06831

Project Objective: The objective of this DCF award is to establish proof-of-concept that gene-corrected patient-derived iPSC can be differentiated into hepatocyte-like cells for treatment of arginase deficiency, an inherited urea cycle disorder.

Investigator:

Name:	Gerald Lipshutz
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Genetic Disorder, Liver Disease, Metabolic Disorders, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: \$1,801,629

Status: Active

Progress Reports

Reporting Period: Year 1

[View Report](#)

Reporting Period: Year 2

[View Report](#)

Reporting Period: Year 4 (NCE)

Grant Application Details

Application Title: Gene therapy-corrected autologous hepatocyte-like cells from induced pluripotent stem cells for the treatment of pediatric single enzyme disorders

Public Abstract: Liver transplantation (LT) has been used to treat a variety of liver diseases. Within hours after birth, neonates can present with disorders of the urea cycle (UCDs), the critical metabolic liver pathway needed to detoxify waste nitrogen from the diet and cellular turnover. The overall incidence of UCDs is estimated to be 1 in 8200 births. An increase in ammonia concentrations is particularly toxic to the central nervous system (CNS), causing brain edema, with multiple episodes affecting survival and often resulting in mental retardation and cerebral palsy. While LT is recommended in neonatal-onset patients with these single-enzyme defects, organ availability is a major limitation and transplantation requires lifelong immunosuppression. In addition, transplant morbidity and mortality are not inconsequential: 1-year survival is about 91.9%, and 5-year survival in children transplanted at less than 5 kg is 74%. Transplantation of genetically corrected embryonic stem cell-derived hepatocytes from the affected patients themselves is a potential way to replace LT for the treatment of metabolic liver disease and will likely not require immunosuppression; importantly, the supply will be limitless, allowing early transplantation before CNS injury. We propose to explore this approach by using a new and robust liver repopulation UCD mouse to advance this therapy: treatment of single-enzyme liver defects with patient-derived and genetically corrected stem cell-induced liver cells.

Statement of Benefit to California: Unfortunately there is a substantial wait for people in California who need a liver transplant, resulting in many who develop significant disability or die while waiting. While many are adults with chronic disease, some are children with metabolic disorders including urea cycle disorders (UCDs).

UCDs are caused by mutations resulting in enzyme deficiencies responsible for removing waste nitrogen, which as ammonia can cause irreversible brain damage, coma and/or death. Newborns can become catastrophically ill within 36-48 hours after birth. These and other inborn errors represent a substantial cause of brain damage and death among newborns and infants and because many cases remain undiagnosed, or infants with the disorders die without a definitive diagnosis, the exact incidence is unknown and likely underestimated.

Present treatment is dietary for most which is onerous & incomplete; definitive therapy is liver transplantation which is challenging in infants who have greater rates of complications and morbidity. In this proposal we will develop genetically-corrected hepatocyte-like cells from induced pluripotent stem cells from patients with arginase deficiency, a UCD. These will be tested for the ability to correct the disorder in a unique UCD liver repopulation animal model. The advantage of the proposed methodology over current therapy is that genetically-corrected cells will be limitless and will require no major surgery or immunosuppression and its short- & long-term risks.

Source URL: <https://www.cirm.ca.gov/our-progress/awards/gene-therapy-corrected-autologous-hepatocyte-cells-induced-pluripotent-stem>